m/H

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
D079.001.02		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 99/ 03811	17/11/1999	24/12/1998
Applicant		
DERMATECH LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rul 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [X] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/03811

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 276561	A	03-08-1988	JP	2107853 C	06-11-1996
			JP	7094394 B	11-10-1995
			JP	63159318 A	02-07-1988
			AU	585739 B	22-06-1989
			AU	8297387 A	30-06-1988
			DD	266506 A	05-04-1989
			DK	683987 A	25-06-1988
			EG	18328 A	30-10-1992
			FI	875703 A	25-06-1988
			HU	45894 A,B	28-09-1988
			IL	84860 A	16-02-1992
			KR	9005854 B	13-08-1990
			NO	875419 A	27-06-1988
			NZ	223056 A	28-11-1989
			PH	23817 A	23-11-1989
			PL	269636 A	13-10-1988
			PT	86437 A,B	01-01-1988
			ZA	8709645 A	30-08-1989
WO 9205811	A	16-04-1992	AT	137979 T	15-06-1996
			AU	649732 B	02-06-1994
			AU	8629591 A	28-04-1992
			CA	2093321 A,C	06-04-1992
			DE	69119598 D	20-06-1996
			DE	69119598 T	12-09-1996
			DK	551349 T	30-09-1996
			EP	0551349 A	21-07-1993
			ES	2090355 T	16-10-1996
			GB	2249956 A,B	27-05-1992
			GR	3019929 T	31-08-1996
			JP	2543457 B	16-10-1996
			JP	6501932 T	03-03-1994
			NO	302400 B	02-03-1998
			NZ	240091 A	25-06-1993
			US	5352457 A	04-10-1994
			ZA	9107959 A	30-12-1992
WO 9210231	A	25-06-1992	US	5164190 A	17-11-1992
			US	5152997 A	06-10-1992
			AU	651165 B	14-07-1994
			AU	9175791 A	08-07-1992
			CA	2098195 A,C	11-06-1992
			EP	0562041 A	29-09-1993
			JP	6503252 T	14-04-1994
			PT	99751 A,B	31-01-1992
			ZA	9109761 A	28-10-1992
EP 569338	A	10-11-1993	US	5665377 A	09-09-1997
			AT	169213 T	15-08-1998
			AU	670273 B	11-07-1996
			AU	3845993 A	11-11-1993
			CA	2095789 A	09-11-1993
			DE	69320096 D	10-09-1998
			DE	69320096 T	10-12-1998
			ES	2121975 T	16-12-1998
			JP	2960832 B	12-10-1999
			JP	6014986 A	25-01-1994
			NZ	247549 A	21-12-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
[redacted]GB 99/03811

Patent document cited in search report	Publication date	Patent family member(s)	Publication dat
EP 569338 A		ZA 9303180 A	14-06-1994
EP 483370 A	06-05-1992	DE 69108512 D	04-05-1995
		DE 69108512 T	03-08-1995
		AT 120368 T	15-04-1995
		AU 633733 B	04-02-1993
		AU 7780091 A	10-12-1991
		CA 2066249 A,C	18-11-1991
		WO 9117752 A	28-11-1991
		JP 2844262 B	06-01-1999
		US 5248676 A	28-09-1993
WO 9809591 A	12-03-1998	US 5985317 A	16-11-1999
		AU 4242797 A	26-03-1998
		BR 9712806 A	23-11-1999
		EP 0952799 A	03-11-1999

INTERNATIONAL SEARCH REPORT

International Application No
P[redacted]B 99/03811

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 276 561 A (PFIZER INC.) 3 August 1988 (1988-08-03) page 2, line 1 - line 5 page 3, line 5 - line 11 page 3, line 25 - line 51 page 5; example 2	1,2,5,6
Y	WO 92 05811 A (ETHICAL PHARMACEULS LIMITED) 16 April 1992 (1992-04-16) the whole document & GB 2 249 956 A cited in the application	1-6
Y	WO 92 10231 A (THERATECH, INC.) 25 June 1992 (1992-06-25) page 2, line 1 - line 9 page 23 -page 27; examples 6-8	1-6

-/—

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 February 2000	06/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Benz, K

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
P[redacted]B 99/03811

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 569 338 A (GIAPHARMA SA) 10 November 1993 (1993-11-10) page 2, line 56 -page 3, line 39	1,4,6
A	EP 0 483 370 A (HISAMITSU PHARMACEUTICAL CO. INC.) 6 May 1992 (1992-05-06) page 3, line 24 - line 27	2,4
A	WO 98 09591 A (THERATECH, INC.) 12 March 1998 (1998-03-12) page 22 -page 24; examples 6,7	1-6

1

PATENT COOPERATION TREATY

15

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
D079.001.02		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/03811	17/11/1999	24/12/1998
International Patent Classification (IPC) or national classification and IPC A61K9/70		
Applicant DERMATECH LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 10 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10/07/2000	12.02.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Hedegaard, A Telephone No. +49 89 2399 8644

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/03811

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-9	as received on	04/10/2000	with letter of	07/09/2000

Claims, No.:

1-7	as received on	04/10/2000	with letter of	07/09/2000

Drawings, sheets:

1/1	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-7
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-7
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Re Section V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: EP-A-0 276 561
D2: WO-A-92 05811
D3: WO-A-92 10231
D4: EP-A-0 569 338
D5: EP-A-0 483 370
D6: WO-A-98 09591

D1 discloses (see p. 2, l. 1-5 and p. 3, l. 25-37) a method of manufacturing a transdermal drug delivery system which comprises mixing the pharmaceutically active substance (piroxicam) with an alkaline agent (see D1, p. 3, l. 12-13). In a preferred embodiment said mixture is thereafter further **dissolved** and dispersed in a solubilizing agent (see D1, p. 3, l. 25-26). The solubilizing agents are exemplified by solvents such as alkylene glycol, glycerine, ethylene glycol monoethyl ether, polyethylene glycol, crotamition and peppermint oil. The amount of said solvent ranges from a solubilizing amount up to about 20 parts by weight of solubilizing agent per one part by weight of piroxicam (see D1, p. 3, l. 35). The resulting solution is mixed with an adhesive in the form of an aqueous dispersion (see D1, p. 3, l. 48).

D2 discloses (see claims 1, 12 and 16) a method of manufacturing a transdermal drug delivery system which comprises dissolving a pharmaceutically active substance in a solvent mixture comprising e.g. diethylene glycol, propylene glycol or glycerol, and mixing the resulting solution with an adhesive in the form of an aqueous dispersion. The mixture is formed into a film which is then dried such that the active ingredient is left in a saturated or supersaturated solution.

D3 discloses (see example 6) a method of manufacturing a transdermal drug delivery system which comprises mixing a pharmaceutically active substance (estradiol) with sorbitan monooleate (a penetration enhancer) and an acrylic

adhesive. At page 2, lines 1-5 of D3 it is disclosed that maximum skin flux occurs when the drug is maintained below saturation in the carrier.

D4 discloses (see examples on p. 3) a method of manufacturing a transdermal drug delivery system which comprises dissolving a pharmaceutically active substance (e.g. estradiol, 2%) in a solvent comprising a penetration enhancer (e.g. lauric acid 10% and propylene glycol 20%) and mixing the resulting solution with an adhesive.

D5 discloses (see p. 3, l. 24-29 and example 1) a method of manufacturing a percutaneous preparation which comprises dissolving estradiol (0.01 parts) in crotamiton (1.00 parts) and mixing with an absorbent polymer.

D6 discloses (see example 6) a method of manufacturing a transdermal drug delivery system which comprises mixing a pharmaceutically active substance with a penetration enhancer (lauryl lactate) and a water-based acrylic adhesive.

2. The subject-matter of claim 1 is not novel (Art. 33(2) PCT) over D1 (see above under item 1). Although it is stated in D1 on page 3, lines 46-49 that the piroxicam is first preferably dissolved in an aqueous solution of the alkaline agent, followed by the addition of the solubilizing agent thereto, this does not exclude the fact that the mixture of piroxicam and alkaline agent is further **dissolved** in a solubilizing agent and, thus, falls within the wording of present claim 1.

The attention is furthermore drawn to D2. Although the final system (after drying) according to D2 is in a saturated or supersaturated solution this does not exclude that the pharmaceutically active substance is firstly dissolved in a ratio less than saturation level and then dried to supersaturation.

3. Claim 6 concerns a product produced by the process. Such a claim is allowable only when the **product as such** is novel and inventive. Transdermal drug delivery systems comprising a pharmaceutically active substance dissolved in a penetration enhancer are known from e.g. D1, D3, D4 and D5 (see above under

item 1). It seems that said systems also fulfil the requirement "in a ratio less than saturation level" (see D1, p. 3, l. 35; D3, p. 2, l. 4; D4, p. 3, l. 43; and D5, p. 4, l. 43). Furthermore, the requirement concerning the ratio as defined in present claim 1 refers to the method and not the final product as such. Claim 6 does not define the ratio in the final product. Consequently, the subject-matter of claim 6 is not considered novel over the documents D1, D3, D4 and D5.

4. In any claims amended to overcome the novelty objection it will be necessary that said claims satisfy the requirements of inventive step (Art. 33(3) PCT).
With regard to the assessment of inventive step the attention is in particular drawn to the document D3 disclosing that maximum skin flux occurs when the drug is maintained below saturation in the carrier.
It is furthermore pointed out that a slight change in the sequence of method steps cannot be considered as involving an inventive step unless this change is followed by unexpected effects.

5. A positive international preliminary report for the subject-matter of the dependent claims 2-5 and 7 can only be established when they refer to independent claims which meet the requirements of the PCT.

Re Section VII

Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D3 is not mentioned in the description, nor are these documents identified therein.

2. Claim 5 contains a reference to the description (the Examples). According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.

3. It appears that examples 8 and 10 after correction no longer fall within the definition of claim 1 since comprising no aqueous solvent based adhesive. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).

TITLE

Transdermal Drug Delivery Systems

DESCRIPTION

Technical Field

The invention relates to transdermal drug delivery systems, that is systems for the administration of medicine through the skin of a patient and into the systemic circulation. In this way, the medicine avoids passing through the gastro-intestinal tract and liver. Thus metabolism is to some extent avoided, and a smaller dose can be used.

Background Art

GB 2249956 contains a useful summary of the state of the art, and discloses such systems containing super-saturated solutions of an active ingredient within an adhesive layer by use of a carefully selected mixture of solvents.

THE INVENTION

The invention provides a method of manufacturing a transdermal drug delivery system which comprises dissolving a pharmaceutically active substance in a ratio less than saturation level in a solvent which is also a skin penetration enhancer, and mixing the resulting solution with an adhesive in the form of an aqueous dispersion or solution. By using the active substance in a ratio less than saturation level, there is a reduced risk of crystallization, a stable system can be manufactured, and a constant rate of delivery to the patient obtained.

It is surprising that certain solvents act both as a skin penetration enhancer and as a solvent for the active substance. Such solvents/enhancers include crotamiton, diethyltoluamide (DEET) and mixtures of two or more thereof. The ratio of crotamiton to diethyltoluamide in such a solvent mixture may be from 5:95 to 95:5% by weight of the total solvent/enhancer ~~solvent~~ content depending on the delivery rate and extent of delivery required for the active substance. By choosing a solvent/enhancer or solvents/enhancers having a boiling point higher than any drying temperature applied to the system, and controlling the drying temperature, the solvent(s) do not evaporate, the solution of the active substance never becomes saturated, and a high proportion of active substance remains in the

system. The active substance/solvent(s) solution can be maintained at 20°-30°C for over one month.

The system is generally presented on a backing sheet and protected up to use by a release liner.

The pharmaceutically active substance may be:
α-Adrenergic agonists such as Adrafinil, Adrenolone, Amidephrine, Aproclonidine, Clonidine, Ephedrine, Naphasoline and Tramazoline;
ß-Adrenergic agonists such as Albuterol, Clenbuterol, Clorprenaline, Methoxyphenamine and Terbuterol;
α-Adrenergic blockers such as Amosulalol, Dapiprasol, Ergoloid Mesylates, Prazosin, Terazosin, Yohimbine;
ß-Adrenergic blockers such as Acebutolol, Alprenolol, Atenolol, Pindolol, Propanolol and Timolol;
Anabolics such as Androstenediol, Ethylstrenol, Methandriol, Nandrolone, Oxymesterone, Quinbolone and Stenbolone;
Analgesic (narcotic) such as Alfentanil, Benzylmorphine, Buprenorphine, Codeine, Codeine Phosphate, Dihydrocodeine, Dihydromorphine, Fentanyl, Methadone Hydrochloride, Morphine, Morphine Derivatives, Narceine, Opium, Oxycodone, Oxymorphone, Phenazocine and Sufentanil;
Analgesics (non-narcotic) such as Acetaminophen, Acetanilide, Acetylsalicyclic Acid, Carbamazepine, Diflunisal, Indomethacin, Ketoprofen, Naproxen, Phenacetin, Salicylamide and Tramadol;
Androgens such as Mesterolone, 17-Methyltestosterone, Testosterone and Testosterone Propionate;
Anaesthetics such as Amylocaine Hydrochloride, Bupivacaine, Lidocaine, Midazolam, Procaine, Tetracaine Hydrochloride, Thiopental Sodium and Zolamine;
Anti-acne drugs such as Algestone Acetophenide, Benzoyl Peroxide, Cyproterone, Resorcinol, Retinoic Acid and Tetroquinolone;
Anti-amebic such as Chloroquine, Chlortetracycline, Dehydroemetine, Emetine, Teclosan, Thiocarbamizine and Tinidazole;
Antianginals such as Alprenolol, Amlodipin Diltiazem, Felodipine, Isosorbide Dinitrate, Nicardipine, Nifedipine, Nitroglycerin, Oxprenolol, Pindolol, Timolol and Verapamil;

Antibacterial drugs such as Gentamicin, Kanamycin, Neomycin, Chloramphenicol, Chloramphenicol Pantothenate, Clindamycin, Lincomycin, Clarithromycin, Erthromycin and Cycloserine;

Anti-estrogens such as Delmadinone Acetate, Tamoxifen and Toremifene;

Antifungal drugs such as Clotrimazole, Econazole, Ketoconazole, Miconazole and Potassium Iodide;

Antihistamines such as Chlorpheniramine, Dimethindene, Pheniramine, Triprolidine and Phenothiazine;

Antihypertensive drugs such as Captopril, Enalapril, Clonidine and Minoxidil;

Anti-inflammatory drugs such as Mefenamic Acid, Flubiprofen, Ibuprofen, Indomethacin, Ketoprofen, Aspirin, Mesalamine, Olsalasine, Piroxicam and Tenoxicam;

Anti-parkinsonian drugs such as Amantadine, Levodopa, Pergolide and Pridinol;

Antipyretics such as Camphor, Menthol, Phenol, Polidocanol, Spirit of Camphor and Trimeprazine;

Anti-seborrheic drugs such as Pyrithione, Resorcinol, Selenium Sulphides and Tioxolone;

Antiseptics such as Chlorhexidine, Bismuth Iodide Oxide, Povidone Iodine, Triclosan, Triclosane Potassium, Carvacrol, p-Cresol, Chloroxine, Halquinol, Boric Acid, α-Terpineol and Chlorhexidine;

Anti-ulcerative drugs such as Cimetidine, Enprostil, Omeprasol, Ranitidine and Trimoprostil;

Anxiolytic drugs such as Buspirone, Bromazepam, Diazepam, Loxapine, and Meprobamate;

Chlorinergic agents such as Bethanechol Chloride, Physostigmine and Pyridostigmine Bromide;

Depigmentors such as Hydroquinine, Hydroquinone and Monobenzone;

Estrogens such as Benzestrol, Dienestrol, Diethylstilbestrol, Dimestrol, Methestrol, Conjugated estrogenic Hormones, Equilenin, Equilin, Estradiol, EstradiolBenzoate, Estradiol 17ß-Cypionate, Estriol, Estrone, Ethinyl Estradiol, Mestranol, Moxestrol, Quinestradiol and Quinestrol;

Gonadotropic hormones such as LH and PMSG;

Nootropic agents such as Aceglutamide, Antiracetam, Piracetam, Pyritinol and Tacrine.

Progestogens such as Allylestrenol, Anagestone, Chlormadinone Acetate, Delmadinone Acetate, Demegestone, Desogestrel, Dimethisterone,

Dydogesterone, Ethisterone, Ethynodiol, Flurogestone Acetate, Gestodene, Gestodene Caprolate, Haloprogesterone, 17-Hydroxy-16-methylene-progesterone, 17α-Hydroxyprogesterone, 17-α-Hydroxygesterone Caprolate, Lynestrenol, Medrogestone, Medroxyprogesterone, Megestrol Acetate, Melengestrol, Norethisterone, Norethisterone Acetate, Noretynodrel, Norgesterone, Norgestimate, Norgestrel, Norgestrienone, Norvinistyerone, Pentagestrone, Progesterone, Promegestone, Quingestrone and Trengestone;

Respiratory stimulants such as Almitrine, Doxapram, Lobeline, Sodium Succinate and Tacrine;

Vitamins, vitamin sources and vitamin extracts such as Vitamins A, B, C, D, E and K and derivatives thereof, Calciferols, Glycyrrhiza and Mecobalamin; or

Vulnerary agents such as Acetylcysteine, Allantoin, Asiaticoside, Cadexomer Iodine, Chitin, Dextranomer and Oxaceprol.

The solvent/enhancer can be Crotamiton, Diethyltoluamide (DEET), Transcutol (Diethylene glycol monoethyl ether), Labrafil M1944CS (unsaturated polyglycolysed glycerides), Labrasol (Glyceryl and polyethylene glycol esters), Tea-tree oil (Oil of Melaleuca), Propylene Glycol, MP DIOL (2-Methyl-1,3- Propanediol) or Polyetheylen Glycol.

It will be appreciated that the amount of active substance to be incorporated in the delivery system is dependent or governed by the drug composition and/or concentration, the desired therapeutic effect for a patient, and the period for which the delivery system is to provide a therapeutic drug level. Preferably, the active substance is present in an amount from 0.1% to 50% by weight of the coating material (i.e. an aqueous emulsion or adhesive solution). More preferably, 0.3% to 30% by weight of the coating material.

The adhesive can be an acrylate, silicone or polyisobutylene. The active substance is generally incorporated in the solvent/enhancer at room temperature (25°C or below) and in a ratio less than 90% of saturation level to prevent crystal formation during storage. Dissolution may be aided by sonication or warming. The resulting solution can be added slowly to the adhesive which may be in the form of an aqueous dispersion or solution, and mixed. An adhesive thickener may be added

to the mixture at about a 50% solution/water mix to produce a thicker spreading solution for reverse roll coating or knife over roll coating.

The resulting delivery system may then be coated onto a release liner, which may be a siliconised polyester such as type FL 2000 (commercially available), or paper, which naturally is impermeable to the active substance. The system can then be dried by circulating hot air, and laminated onto a backing sheet, which may be a 3M Health Care Type 1220, the backing sheet naturally being impermeable to the active substance. The layer may be coated to a wet-coat thickness of from 20 to 500μm. Alternatively, the delivery system mixture may be spread or coated onto the backing sheet, and then laminated to the release liner. The hot air circulation may be effected at gradually increased temperatures from 50°C to 140°C.

DRAWING

Fig. 1 is section through an adhesive tape for application to the skin of a patient comprising a drug delivery system according to the invention. A delivery system comprising an active substance, adhesive and solvent/skin penetration enhancer 4 is coated as a layer onto a siliconized release paper 2 and laminated onto a backing strip 6.

The following Examples of ingredients in parts by weight may be used in the production of delivery systems as described above:

	Eg 1	Eg 2	Eg 3	Eg 4	Eg 5
Estradiol Hemihydrate	1.0	1.0	1.0	1.0	0.9
Norethisterone Acetate	2.0	2.4	2.4	2.4	2.4
DEET	-	-	-	18.0	15.3
Crotamiton	-	18.0	20.0	-	2.7
Labrafil M (1944CS)	5.0	4.25	-	-	-
Transcutol	20.0	-	-	-	-
Lauroglycol	4.0	-	-	-	-
Labrasol	4.0	-	-	-	-
Monsanto 3011	64.00	74.35	-	-	-
Monsanto 2484			76.6	78.6	-
Monsanto 2397	-	-	-	-	-
C945/127		-	-	-	78.7
NS 2287	-	-	-	-	-
Acrysol ASE60	-	-	-	-	-
Ammonia BP (aq.dil)	qs	qs	qs	qs	-
Purified water (BP)	qs	qs	qs	qs	qs

	Eg 6	Eg 7	Eg 8	Eg 9	Eg 10	Eg 11
Estradiol Hemihydrate	0.9	0.9	0.9	1.2	1.1	1.0
Norethisterone Acetate	2.4	2.4	2.4	-	-	-
DEET	9.0	2.7	15.3	-	6.0	6.09
Crotamiton	9.0	15.3	2.7	7.5	0.6	-
Labrafil M(1944CS)	-	-	-	2.0	-	-
Transcutol	-	-	-	-	-	-
Lauroglycol	-	-	-	-	-	-
Labrasol	-	-	-	-	-	-
Monsanto 3011	-	-	-	-	-	-
Monsanto 2484	-	-	-	-	-	-
Monsanto 2397	-	-	-	89.3	-	-
C945/127	78.7	78.7		-	-	93.77
NS 2287	-	-	78.7	-	92.3	-
Acrysol ASE60	-	-	-	-	-	0.2-0.9
Ammonia BP (aq.dil)	-	-	-	-	-	qs
Purified water (BP)	qs	qs	~~qs~~	qs	~~qs~~	qs

Manufacturing Method (illustrative)

A) Delivery System using adhesive - aqueous emulsion

The active substance is dissolved in the solvent/enhancer by means of heating and mixing over a 45°-55°C water bath with agitation. When the solution is optically clear, it is checked microscopically for absence of crystals.

The adhesive is weighed into a separate mixing vessel, diluted with water if necessary over a period not exceeding 30 mins to achieve the requisite viscosity. The active substance/solvent solution is gradually added to the adhesive solution with mixing. The pH is adjusted to 6.5-7.5 and a thickener is added (if appropriate) to obtain a suitable viscosity (eg 900-100 cps) for the selected coating process such as reverse roll coating or knife over roll coating.

The resultant aqueous emulsion is coated onto a release liner (typical coating thickness 20-500μm), and dried by passing in sequence through ovens at 50-140°C. The product is then laminated onto a backing sheet.

B) Delivery system using an adhesive solution

The active substance is dissolved in a solvent/enhancer by means of heating and mixing as described above. The adhesive is weighed in a separate vessel and the active substance/solvent solution is gradually added to the solution of adhesive with mixing. The resultant adhesive solution is coated onto a release liner, dried by passing in sequence through ovens at 50-140°C. The product is then laminated onto a backing sheet.

In-vitro drug delivery through the skin

In-vitro skin permeation experiments with human skin have been on systems made from the above ingredients carried out using Franz-type diffusion cells, and the studies were carried out on a Hanson Microette system.

Dermatomed human skin sections were mounted onto the Franz cells and transdermal drug delivery systems mounted on tape backings (1.5cm^2) were placed on the stratum corneal surface of the skin. Each Franz cell contained 7ml of ethanol phosphate buffered saline as the receptor medium, maintained at 32°C. At predetermined time intervals 0.7ml of the receptor solution was sampled and an equal amount replaced.

The samples were analysed by High Pressure Liquid Chromatography.

The skin mass transport of Estradiol and Norethisterone Acetate has been found to be enhanced by the solvent/skin penetration enhancer DEET and/or Crotamiton in a concentration below saturation. Further, the active substance flux profile follows the solvent flux profile, the latter showing high skin penetration flux during the first 20 hours of application.

Indications

The main indications are in both peri-menopausal and menopausal women for the control in the former of the symptoms of the menopause such as hot flushes, sweating and the other symptoms of the peri-menopause,

and in the case of the menopause the prevention of osteoporosis and cardiac events such as coronary thrombosis.

CLAIMS

1. A method of manufacturing a transdermal drug delivery system which comprises dissolving a pharmaceutically active substance in a ratio less than saturation level in a solvent which is also a skin penetration enhancer, and mixing the resulting solution with an adhesive in the form of an aqueous dispersion or solution.

2. A method according to claim 1 in which the solvent/enhancer includes crotamiton.

3. A method according to claim 1 or claim 2 in which the solvent includes DEET.

4. A method according to any preceding claim in which the active substance includes estradiol.

5. A transdermal drug delivery system manufactured by a method according to any preceding claim.

6. A transdermal drug delivery system according to claim 5 in which the active substance is present in said aqueous dispersion or solution from 0.1% to 50% by weight.

WHAT IS CLAIMED IS:

1. A method for the manufacture of a transdermal drug delivery system, which comprises the successive steps of :

(a) dissolving a pharmaceutically active substance in a solvent comprising at least one skin penetration enhancer selected from the group consisting of crotamicon and diethyltoluamide (DEET) to form a solution at a concentration less than saturation;

(f) mixing said solution with an adhesive in the form of a solution or an aqueous dispersion;

(g) forming the mixture obtained in step (b) into a film on one of a release liner and a backing sheet; and

(d) drying said film at a temperature less than the boiling point of the skin penetration enhancer(s) used as solvent in step (a).

2. A method according to claim 1 wherein the solvent used in step (a) comprises crotamicon and DEET in a ratio of from 5:95% to 95:5% by weight.

3. A method according to claim 1 wherein the solvent used in step (a) additionally comprises at least one other skin penetration enhancer.

4. A method according to claim 3 wherein said at least one other skin penetration enhancer is selected from the group consisting of transcutol (diethylene glycol monoethyl ether), Labrafil M1944CS (unsaturated polyglycolysed glycerides), Labrasol (glyceryl and polyethylene glycol esters), lauroglycol (propylene glycol laurate), tee tree oil (oil of Melaleuca), propylene glycol, MP DIOL (2-methyl-1,3-propanediol) and polyethylene glycol.

5. A method according to claim 1 wherein the active substance is dissolved in step (a) in the skin penetration enhancer(s) to form a solution at a concentration of less than 90% of saturation.

6. A method according to claim 1 wherein the active substance is estradiol.

7. A method according to claim 1 wherein the adhesive is selected from the group consisting of acrylate, polyisobutylene and silicone adhesives.

8. A method according to claim 1 wherein the film is formed in step (c) on a release liner and the film, after drying in step (d), is laminated on to a backing sheet.

9. A method according to claim 1 wherein the film is formed in step (c) on a backing sheet and the film, after drying in step (d), is laminated on to a release liner.

10. A method according to claim 1 wherein the drying temperature in step (d) is increased gradually from 50°C to 140°C.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

SERJEANTS
25 The Crescent
King Street
Leicester LE1 6RX
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	12.02.2001
Applicant's or agent's file reference D079.001.02	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/03811	17/11/1999	24/12/1998

Applicant
DERMATECH LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Tantum, P Tel.+49 89 2399-8143

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
D079.001.02		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/03811	17/11/1999	24/12/1998
International Patent Classification (IPC) or national classification and IPC		
A61K9/70		
Applicant		
DERMATECH LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 10 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10/07/2000	12.02.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Hedegaard, A Telephone No. +49 89 2399 8644

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/03811

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:

Description, pages:

1-9	as received on	04/10/2000	with letter of	07/09/2000

Claims, No.:

1-7	as received on	04/10/2000	with letter of	07/09/2000

Drawings, sheets:

1/1	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-7
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-7
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	

2. Citations and explanations
   see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Re Section V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: EP-A-0 276 561
D2: WO-A-92 05811
D3: WO-A-92 10231
D4: EP-A-0 569 338
D5: EP-A-0 483 370
D6: WO-A-98 09591

D1 discloses (see p. 2, l. 1-5 and p. 3, l. 25-37) a method of manufacturing a transdermal drug delivery system which comprises mixing the pharmaceutically active substance (piroxicam) with an alkaline agent (see D1, p. 3, l. 12-13). In a preferred embodiment said mixture is thereafter further **dissolved** and dispersed in a solubilizing agent (see D1, p. 3, l. 25-26). The solubilizing agents are exemplified by solvents such as alkylene glycol, glycerine, ethylene glycol monoethyl ether, polyethylene glycol, crotamition and peppermint oil. The amount of said solvent ranges from a solubilizing amount up to about 20 parts by weight of solubilizing agent per one part by weight of piroxicam (see D1, p. 3, l. 35). The resulting solution is mixed with an adhesive in the form of an aqueous dispersion (see D1, p. 3, l. 48).

D2 discloses (see claims 1, 12 and 16) a method of manufacturing a transdermal drug delivery system which comprises dissolving a pharmaceutically active substance in a solvent mixture comprising e.g. diethylene glycol, propylene glycol or glycerol, and mixing the resulting solution with an adhesive in the form of an aqueous dispersion. The mixture is formed into a film which is then dried such that the active ingredient is left in a saturated or supersaturated solution.

D3 discloses (see example 6) a method of manufacturing a transdermal drug delivery system which comprises mixing a pharmaceutically active substance (estradiol) with sorbitan monooleate (a penetration enhancer) and an acrylic

adhesive. At page 2, lines 1-5 of D3 it is disclosed that maximum skin flux occurs when the drug is maintained below saturation in the carrier.

D4 discloses (see examples on p. 3) a method of manufacturing a transdermal drug delivery system which comprises dissolving a pharmaceutically active substance (e.g. estradiol, 2%) in a solvent comprising a penetration enhancer (e.g. lauric acid 10% and propylene glycol 20%) and mixing the resulting solution with an adhesive.

D5 discloses (see p. 3, l. 24-29 and example 1) a method of manufacturing a percutaneous preparation which comprises dissolving estradiol (0.01 parts) in crotamiton (1.00 parts) and mixing with an absorbent polymer.

D6 discloses (see example 6) a method of manufacturing a transdermal drug delivery system which comprises mixing a pharmaceutically active substance with a penetration enhancer (lauryl lactate) and a water-based acrylic adhesive.

2. The subject-matter of claim 1 is not novel (Art. 33(2) PCT) over D1 (see above under item 1). Although it is stated in D1 on page 3, lines 46-49 that the piroxicam is first preferably dissolved in an aqueous solution of the alkaline agent, followed by the addition of the solubilizing agent thereto, this does not exclude the fact that the mixture of piroxicam and alkaline agent is further **dissolved** in a solubilizing agent and, thus, falls within the wording of present claim 1.

   The attention is furthermore drawn to D2. Although the final system (after drying) according to D2 is in a saturated or supersaturated solution this does not exclude that the pharmaceutically active substance is firstly dissolved in a ratio less than saturation level and then dried to supersaturation.

3. Claim 6 concerns a product produced by the process. Such a claim is allowable only when the **product as such** is novel and inventive. Transdermal drug delivery systems comprising a pharmaceutically active substance dissolved in a penetration enhancer are known from e.g. D1, D3, D4 and D5 (see above under

item 1). It seems that said systems also fulfil the requirement "in a ratio less than saturation level" (see D1, p. 3, l. 35; D3, p. 2, l. 4; D4, p. 3, l. 43; and D5, p. 4, l. 43). Furthermore, the requirement concerning the ratio as defined in present claim 1 refers to the method and not the final product as such. Claim 6 does not define the ratio in the final product. Consequently, the subject-matter of claim 6 is not considered novel over the documents D1, D3, D4 and D5.

4. In any claims amended to overcome the novelty objection it will be necessary that said claims satisfy the requirements of inventive step (Art. 33(3) PCT).
With regard to the assessment of inventive step the attention is in particular drawn to the document D3 disclosing that maximum skin flux occurs when the drug is maintained below saturation in the carrier.
It is furthermore pointed out that a slight change in the sequence of method steps cannot be considered as involving an inventive step unless this change is followed by unexpected effects.

5. A positive international preliminary report for the subject-matter of the dependent claims 2-5 and 7 can only be established when they refer to independent claims which meet the requirements of the PCT.

Re Section VII

Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D3 is not mentioned in the description, nor are these documents identified therein.

2. Claim 5 contains a reference to the description (the Examples). According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.

3. It appears that examples 8 and 10 after correction no longer fall within the definition of claim 1 since comprising no aqueous solvent based adhesive. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).

TITLE

Transdermal Drug Delivery Systems

DESCRIPTION

Technical Field

The invention relates to transdermal drug delivery systems, that is systems for the administration of medicine through the skin of a patient and into the systemic circulation. In this way, the medicine avoids passing through the gastro-intestinal tract and liver. Thus metabolism is to some extent avoided, and a smaller dose can be used.

Background Art

GB 2249956 contains a useful summary of the state of the art, and discloses such systems containing super-saturated solutions of an active ingredient within an adhesive layer by use of a carefully selected mixture of solvents.

THE INVENTION

The invention provides a method of manufacturing a transdermal drug delivery system which comprises dissolving a pharmaceutically active substance in a ratio less than saturation level in a solvent which is also a skin penetration enhancer, and mixing the resulting solution with an adhesive in the form of an aqueous dispersion or solution. By using the active substance in a ratio less than saturation level, there is a reduced risk of crystallization, a stable system can be manufactured, and a constant rate of delivery to the patient obtained.

It is surprising that certain solvents act both as a skin penetration enhancer and as a solvent for the active substance. Such solvents/enhancers include crotamiton, diethyltoluamide (DEET) and mixtures of two or more thereof. The ratio of crotamiton to diethyltoluamide in such a solvent mixture may be from 5:95 to 95:5% by weight of the total solvent/enhancer content depending on the delivery rate and extent of delivery required for the active substance. By choosing a solvent/enhancer or solvents/enhancers having a boiling point higher than any drying temperature applied to the system, and controlling the drying temperature, the solvent(s) do not evaporate, the solution of the active substance never becomes saturated, and a high proportion of

active substance remains in the system. The active substance/solvent(s) solution can be maintained at 20°-30°C for over one month.

The system is generally presented on a backing sheet and protected up to use by a release liner.

The pharmaceutically active substance may be:
α-Adrenergic agonists such as Adrafinil, Adrenolone, Amidephrine, Aproclonidine, Clonidine, Ephedrine, Naphasoline and Tramazoline;
ß-Adrenergic agonists such as Albuterol, Clenbuterol, Clorprenaline, Methoxyphenamine and Terbuterol;
α-Adrenergic blockers such as Amosulalol, Dapiprasol, Ergoloid Mesylates, Prazosin, Terazosin, Yohimbine;
ß-Adrenergic blockers such as Acebutolol, Alprenolol, Atenolol, Pindolol, Propanolol and Timolol;
Anabolics such as Androstenediol, Ethylstrenol, Methandriol, Nandrolone, Oxymesterone, Quinbolone and Stenbolone;
Analgesic (narcotic) such as Alfentanil, Benzylmorphine, Buprenorphine, Codeine, Codeine Phosphate, Dihydrocodeine, Dihydromorphine, Fentanyl, Methadone Hydrochloride, Morphine, Morphine Derivatives, Narceine, Opium, Oxycodone, Oxymorphone, Phenazocine and Sufentanil;
Analgesics (non-narcotic) such as Acetaminophen, Acetanilide, Acetylsalicyclic Acid, Carbamazepine, Diflunisal, Indomethacin, Ketoprofen, Naproxen, Phenacetin, Salicylamide and Tramadol;
Androgens such as Mesterolone, 17-Methyltestosterone, Testosterone and Testosterone Propionate;
Anaesthetics such as Amylocaine Hydrochloride, Bupivacaine, Lidocaine, Midazolam, Procaine, Tetracaine Hydrochloride, Thiopental Sodium and Zolamine;
Anti-acne drugs such as Algestone Acetophenide, Benzoyl Peroxide, Cyproterone, Resorcinol, Retinoic Acid and Tetroquinolone;
Anti-amebic such as Chloroquine, Chlortetracycline, Dehydroemetine, Emetine, Teclosan, Thiocarbamizine and Tinidazole;
Antianginals such as Alprenolol, Amlodipin Diltiazem, Felodipine, Isosorbide Dinitrate, Nicardipine, Nifedipine, Nitroglycerin, Oxprenolol, Pindolol, Timolol and Verapamil;

Antibacterial drugs such as Gentamicin, Kanamycin, Neomycin, Chloramphenicol, Chloramphenicol Pantothenate, Clindamycin, Lincomycin, Clarithromycin, Erthromycin and Cycloserine;

Anti-estrogens such as Delmadinone Acetate, Tamoxifen and Toremifene;

Antifungal drugs such as Clotrimazole, Econazole, Ketoconazole, Miconazole and Potassium Iodide;

Antihistamines such as Chlorpheniramine, Dimethindene, Pheniramine, Triprolidine and Phenothiazine;

Antihypertensive drugs such as Captopril, Enalapril, Clonidine and Minoxidil;

Anti-inflammatory drugs such as Mefenamic Acid, Flubiprofen, Ibuprofen, Indomethacin, Ketoprofen, Aspirin, Mesalamine, Olsalasine, Piroxicam and Tenoxicam;

Anti-parkinsonian drugs such as Amantadine, Levodopa, Pergolide and Pridinol;

Antipyretics such as Camphor, Menthol, Phenol, Polidocanol, Spirit of Camphor and Trimeprazine;

Anti-seborrheic drugs such as Pyrithione, Resorcinol, Selenium Sulphides and Tioxolone;

Antiseptics such as Chlorhexidine, Bismuth Iodide Oxide, Povidone Iodine, Triclosan, Triclosane Potassium, Carvacrol, p-Cresol, Chloroxine, Halquinol, Boric Acid, α-Terpineol and Chlorhexidine;

Anti-ulcerative drugs such as Cimetidine, Enprostil, Omeprasol, Ranitidine and Trimoprostil;

Anxiolytic drugs such as Buspirone, Bromazepam, Diazepam, Loxapine, and Meprobamate;

Chlorinergic agents such as Bethanechol Chloride, Physostigmine and Pyridostigmine Bromide;

Depigmentors such as Hydroquinine, Hydroquinone and Monobenzone;

Estrogens such as Benzestrol, Dienestrol, Diethylstilbestrol, Dimestrol, Methestrol, Conjugated estrogenic Hormones, Equilenin, Equilin, Estradiol, EstradiolBenzoate, Estradiol 17ß-Cypionate, Estriol, Estrone, Ethinyl Estradiol, Mestranol, Moxestrol, Quinestradiol and Quinestrol;

Gonadotropic hormones such as LH and PMSG;

Nootropic agents such as Aceglutamide, Antiracetam, Piracetam, Pyritinol and Tacrine.

Progestogens such as Allylestrenol, Anagestone, Chlormadinone Acetate, Delmadinone Acetate, Demegestone, Desogestrel, Dimethisterone,

Dydogesterone, Ethisterone, Ethynodiol, Flurogestone Acetate, Gestodene, Gestodene Caprolate, Haloprogesterone, 17-Hydroxy-16-methylene-progesterone, 17α-Hydroxyprogesterone, 17-α-Hydroxygesterone Caprolate, Lynestrenol, Medrogestone, Medroxyprogesterone, Megestrol Acetate, Melengestrol, Norethisterone, Norethisterone Acetate, Noretynodrel, Norgesterone, Norgestimate, Norgestrel, Norgestrienone, Norvinistyerone, Pentagestrone, Progesterone, Promegestone, Quingestrone and Trengestone;

Respiratory stimulants such as Almitrine, Doxapram, Lobeline, Sodium Succinate and Tacrine;

Vitamins, vitamin sources and vitamin extracts such as Vitamins A, B, C, D, E and K and derivatives thereof, Calciferols, Glycyrrhiza and Mecobalamin; or

Vulnerary agents such as Acetylcysteine, Allantoin, Asiaticoside, Cadexomer Iodine, Chitin, Dextranomer and Oxaceprol.

The solvent/enhancer can be Crotamiton, Diethyltoluamide (DEET), Transcutol (Diethylene glycol monoethyl ether), Labrafil MI944CS (unsaturated polyglycolysed glycerides), Labrasol (Glyceryl and polyethylene glycol esters), Tea-tree oil (Oil of Melaleuca), Propylene Glycol, MP DIOL (2-Methyl-1,3- Propanediol) or Polyetheylen Glycol.

It will be appreciated that the amount of active substance to be incorporated in the delivery system is dependent or governed by the drug composition and/or concentration, the desired therapeutic effect for a patient, and the period for which the delivery system is to provide a therapeutic drug level. Preferably, the active substance is present in an amount from 0.1% to 50% by weight of the coating material (i.e. an aqueous emulsion or adhesive solution). More preferably, 0.3% to 30% by weight of the coating material.

The adhesive can be an acrylate, silicone or polyisobutylene. The active substance is generally incorporated in the solvent/enhancer at room temperature (25°C or below) and in a ratio less than 90% of saturation level to prevent crystal formation during storage. Dissolution may be aided by sonication or warming. The resulting solution can be added slowly to the adhesive which may be in the form of an aqueous dispersion or solution, and mixed. An adhesive thickener may be added

to the mixture at about a 50% solution/water mix to produce a thicker spreading solution for reverse roll coating or knife over roll coating.

The resulting delivery system may then be coated onto a release liner, which may be a siliconised polyester such as type FL 2000 (commercially available), or paper, which naturally is impermeable to the active substance. The system can then be dried by circulating hot air, and laminated onto a backing sheet, which may be a 3M Health Care Type 1220, the backing sheet naturally being impermeable to the active substance. The layer may be coated to a wet-coat thickness of from 20 to 500μm. Alternatively, the delivery system mixture may be spread or coated onto the backing sheet, and then laminated to the release liner. The hot air circulation may be effected at gradually increased temperatures from 50°C to 140°C.

DRAWING

Fig. 1 is section through an adhesive tape for application to the skin of a patient comprising a drug delivery system according to the invention. A delivery system comprising an active substance, adhesive and solvent/skin penetration enhancer 4 is coated as a layer onto a siliconized release paper 2 and laminated onto a backing strip 6.

The following Examples of ingredients in parts by weight may be used in the production of delivery systems as described above:

	Eg 1	Eg 2	Eg 3	Eg 4	Eg 5
Estradiol Hemihydrate	1.0	1.0	1.0	1.0	0.9
Norethisterone Acetate	2.0	2.4	2.4	2.4	2.4
DEET	-	-	-	18.0	15.3
Crotamiton	-	18.0	20.0	-	2.7
Labrafil M (1944CS)	5.0	4.25	-	-	-
Transcutol	20.0	-	-	-	-
Lauroglycol	4.0	-	-	-	-
Labrasol	4.0	-	-	-	-
Monsanto 3011	64.00	74.35	-	-	-
Monsanto 2484			76.6	78.6	-
Monsanto 2397	-	-	-	-	-
C945/127		-	-	-	78.7
NS 2287	-	-	-	-	-
Acrysol ASE60	-	-	-	-	-
Ammonia BP (aq.dil)	qs	qs	qs	qs	-
Purified water (BP)	qs	qs	qs	qs	qs

	Eg 6	Eg 7	Eg 8	Eg 9	Eg 10	Eg 11
Estradiol Hemihydrate	0.9	0.9	0.9	1.2	1.1	1.0
Norethisterone Acetate	2.4	2.4	2.4	-	-	-
DEET	9.0	2.7	15.3	-	6.0	6.09
Crotamiton	9.0	15.3	2.7	7.5	0.6	-
Labrafil M(1944CS)	-	-	-	2.0	-	-
Transcutol	-	-	-	-	-	-
Lauroglycol	-	-	-	-	-	-
Labrasol	-	-	-	-	-	-
Monsanto 3011	-	-	-	-	-	-
Monsanto 2484	-	-	-	-	-	-
Monsanto 2397	-	-	-	89.3	-	-
C945/127	78.7	78.7		-	-	93.77
NS 2287	-	-	78.7	-	92.3	-
Acrysol ASE60	-	-	-	-	-	0.2-0.9
Ammonia BP (aq.dil)	-	-	-	-	-	qs
Purified water (BP)	qs	qs	-	qs	-	qs

Manufacturing Method (illustrative)

A) Delivery System using adhesive - aqueous emulsion

The active substance is dissolved in the solvent/enhancer by means of heating and mixing over a 45°-55°C water bath with agitation. When the solution is optically clear, it is checked microscopically for absence of crystals.

The adhesive is weighed into a separate mixing vessel, diluted with water if necessary over a period not exceeding 30 mins to achieve the requisite viscosity. The active substance/solvent solution is gradually added to the adhesive solution with mixing. The pH is adjusted to 6.5-7.5 and a thickener is added (if appropriate) to obtain a suitable viscosity (eg

900-1000 cps) for the selected coating process such as reverse roll coating or knife over roll coating.

The resultant aqueous emulsion is coated onto a release liner (typical coating thickness 20-500 μm), and dried by passing in sequence through ovens at 50-140°C. The product is then laminated onto a backing sheet.

B) Delivery system using an adhesive solution

The active substance is dissolved in a solvent/enhancer by means of heating and mixing as described above. The adhesive is weighed in a separate vessel and the active substance/solvent solution is gradually added to the solution of adhesive with mixing. The resultant adhesive solution is coated onto a release liner, dried by passing in sequence through ovens at 50-140°C. The product is then laminated onto a backing sheet.

In-vitro drug delivery through the skin

In-vitro skin permeation experiments with human skin have been on systems made from the above ingredients carried out using Franz-type diffusion cells, and the studies were carried out on a Hanson Microette system.

Dermatomed human skin sections were mounted onto the Franz cells and transdermal drug delivery systems mounted on tape backings (1.5cm^2) were placed on the stratum corneal surface of the skin. Each Franz cell contained 7ml of ethanol phosphate buffered saline as the receptor medium, maintained at 32°C. At predetermined time intervals 0.7ml of the receptor solution was sampled and an equal amount replaced.

The samples were analysed by High Pressure Liquid Chromatography.

The skin mass transport of Estradiol and Norethisterone Acetate has been found to be enhanced by the solvent/skin penetration enhancer DEET and/or Crotamiton in a concentration below saturation. Further, the active substance flux profile follows the solvent flux profile, the latter showing high skin penetration flux during the first 20 hours of application.

Indications

The main indications are in both peri-menopausal and menopausal women for the control in the former of the symptoms of the menopause such as hot flushes, sweating and the other symptoms of the peri-menopause, and in the case of the menopause the prevention of osteoporosis and cardiac events such as coronary thrombosis.

CLAIMS

1. A method of manufacturing a transdermal drug delivery system which comprises dissolving a pharmaceutically active substance in a ratio less than saturation level in a solvent which is also a skin penetration enhancer, and mixing the resulting solution with an adhesive in the form of an aqueous dispersion or solution.

2. A method according to claim 1 in which the solvent/enhancer includes crotamiton.

3. A method according to claim 1 or claim 2 in which the solvent includes DEET.

4. A method according to any preceding claim in which the active substance includes estradiol.

5. A method of manufacturing a transdermal drug delivery system substantially as herein described in any of the Examples.

6. A transdermal drug delivery system manufactured by a method according to any preceding claim.

7. A transdermal drug delivery system according to claim 6 in which the active substance is present in said aqueous dispersion or solution from 0.1% to 50% by weight.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 10 August 2000 (10.08.00)	
International application No. PCT/GB99/03811	**Applicant's or agent's file reference** D079.001.02
International filing date (day/month/year) 17 November 1999 (17.11.99)	**Priority date** (day/month/year) 24 December 1998 (24.12.98)
Applicant SOLOMON, Montague, Cecil et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

10 July 2000 (10.07.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38